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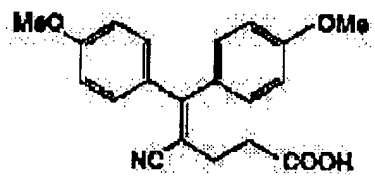
(54) SUPPRESSING AGENT FOR VASCULARIZATION

(57)Abstract:

PURPOSE: To obtain an agent for the prevention, treatment and improvement of the diseases such as a solid cancer, a keloid and an inflammation for which a suppressing action for vascularization is effective, by containing satigrel and/or aspirin or their salts as active ingredients, and high in safety and usefulness.

CONSTITUTION: This suppressing agent for vascularization contains at least one kind selected from satigrel of the formula or aspirin, or their salts as active ingredients. The clinical dosage of satigrel or aspirin is preferably 1-1000mg daily for an adult. Specifically, a preparation for the injection of satigrel is obtained e.g. by dissolving 1mg satigrel sodium, 1mg mannitol and the suitable amount of citric acid for one vial with a distilled water for injection or a saline, adjusting pH with citric acid, aseptically filtering, and then lyophilizing.



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* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to prevention and therapy / improvement agents, such as the gastric cancer and lung cancer based on the depressant action of the vascularization, hepatic carcinoma, colon cancer, colon cancer, rectal cancer, a pancreatic cancer, a prostatic cancer, vesical cancer, kidney cancer, an ovarian cancer, a uterine cancer, a breast cancer, skin carcinoma, malignant **** or a basal cell carcinoma, keloid, inflammation, or diabetic retinopathy.
[0002]
[Background of the Invention] The vascularization is widely accepted in extraphysiologic processes, such as growth of a solid neoplasm, and wound healing, from vasoganglion formation of fetus. It was found out that fibroblast specializes to an endothelial cell in recent years, and a new blood vessel is formed although it was thought that the mechanism was conventionally based on the existing venule, the migration of the vascular endothelial cell from a capillary, growth, or lumen formation. Such vascularization is especially concerned with diseases, such as a solid neoplasm and keloid, deeply.
[0003] The inclination which attaches importance to the quality of life (quality of a life and survival) maintaining the effectiveness which is increasing in whole company meeting and changes to the strong drugs of a side effect like the conventional anticancer agent, an anticancer agent, a cancer growth inhibitor, or an anticancer drug in a disease therapy or medical treatment in recent years, even if it carried out chronic administration, drugs with high safety were called for.
[0004] Moreover, effect great as a physical or mental sequela remains, and the keloid formed in the process of wound healing, such as a burn, also has big influence also in the social activity after recovery. Then, according to the reason for pursuing the quality of life like the above, high prevention and therapy / improvement agent of usefulness was called for.
[0005] Furthermore, although it was known that the vascularization is involving also in inflammation or diabetic retinopathy, the actual condition is that there is no effective remedy, and high prevention and therapy / improvement agent of usefulness was called for.
[0006]
[Description of the Prior Art] For example, it is indicated by WO 94/No. 14851 official report that 2-O and 3-O-DESURUFEITEDDO (Desulfated) heparin is effective in vascularization control.
[0007] Moreover, it is indicated by the Patent Publication table No. 506702 [six to] official report, or the Patent Publication table No. 509116 [six to] official report that the fourth factor of a platelet obtained by gene recombination etc. or its related polypeptide is effective in vascularization control.
[0008] Furthermore, it is indicated that a tetrahydrothieno pyridine derivative is effective in EP-No. 499544 official report similarly.
[0009]
[Problem(s) to be Solved by the Invention] Although the 2-O and 3-O-DESURUFEITEDDO (Desulfated) heparin currently indicated by WO 94/No. 14851 official report was the derivative of the heparin which is an anticoagulant, in paths other than an intravenous injection, heparin could not be

prescribed for the patient and had the side effect carried out that it is easy to produce bleeding. Moreover, by 2-O and 3-O-, SURUFEITEDDO (Desulfated) heparin itself is a new molecular entity, and clinical effectiveness and safety were not checked at all.

[0010] Next, also about the fourth factor of a platelet currently indicated by the Patent Publication table No. 506702 [six to] official report, or the Patent Publication table No. 509116 [six to] official report, or its related polypeptide, since it was protein, in paths other than an intravenous injection, a medicine could not be prescribed for the patient, and clinical effectiveness and safety were not checked at all, but also had fear of an anaphylactic shock.

[0011] Moreover, although it was thought in the tetrahydrothieno pyridine derivative currently indicated by EP-No. 499544 official report that internal use became possible, it is a new molecular entity too and clinical effectiveness and safety were not checked at all.

[0012] Safety was high on the basis of such a background, and it was expected strongly prevention and therapy / improvement agents, such as the high vascularization inhibitor, especially the various solid carcinota of usefulness, keloid, inflammation, or diabetic retinopathy.

[0013]

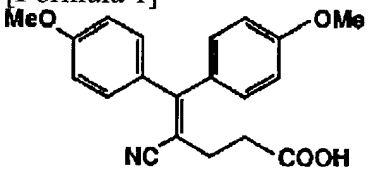
[Means for Solving the Problem] Then, this invention persons have inquired wholeheartedly about the compound equipped with the aforementioned requirements. Consequently, as a platelet aggregation inhibitor, vascularization depressant action found out attaining the desired end as a prevention and therapy / improvement agent of an effective disease, and one or more sorts chosen from SACHIGURERU or aspirin used widely clinical or the salt of those permitted in pharmacology already completed this invention.

[0014] Therefore, the object of this invention is to offer high prevention and therapy / improvement agent of the clinical usefulness in the gastric cancer and lung cancer based on depressant action, the hepatic carcinoma, the colon cancer, the colon cancer, the rectal cancer, the pancreatic cancer, the prostatic cancer, the vesical cancer, the kidney cancer, the ovarian cancer, the uterine cancer, the breast cancer, the skin carcinoma, malignant **** or a basal cell carcinoma, keloid, inflammation, or diabetic retinopathy of the vascularization etc.

[0015] It is indicated as SACHIGURERU (Satigrel, INN library-name) concerning this invention by JP,63-10743,A. It is 4-Cyano-5 and 5-bis(4-methoxyphenyl)-4-pentanoic acid (CAS registration number; 111753-73-2), and is a platelet aggregation inhibitor under manufacturing approval application expressed with the following chemical formula.

[0016]

[Formula 1]



[0017] Moreover, although the salt permitted in pharmacology will not be limited if SACHIGURERU and a salt are formed, it can specifically mention the addition salt of alkaline earth metal, such as an addition salt of alkali metal, such as sodium salt, potassium salt, and lithium salt, a calcium salt, and magnesium salt, the addition salt of an amine, the addition salt of amino acid, etc.

[0018] next, the aspirin (Aspirin) concerning this invention -- CAS registration number 50-78-2 it is -- it is a platelet aggregation inhibitor or an antipyretic, and salts, such as sodium salt, may be formed.

[0019] Then, the acute toxicity test result of SACHIGURERU is shown as an example of representation of this invention compound.

[Acute toxicity test] 7-8 Week-old Slc:SD a rat -- and -- Single-dose toxicity study according a Slc:ICR mouse to taking orally, intraperitoneal, and subcutaneous administration was carried out using each five group sexes each. (Intraperitoneal and the medium of subcutaneous administration; physiological saline) A fifty percent lethal dose value is summarized at the following table.

[0020]
[A table 1]
サチグレルの急性毒性 (LD_{50}; mg/Kg)

投与経路	マウス		ラット	
	雄	雌	雄	雌
経口	940	891	436	337
腹腔	342	379	264	220
皮下	1140	839	445	495

[0021] These A fifty percent lethal dose value is about 500 or more times of the clinical dosage in intravenous administration, and safety is very high.
[0022] Next, as an administration pharmaceutical form of this invention compound, external preparations and injection pharmaceutical preparation, such as oral pharmaceutical preparation, such as powder, a fine grain agent, a granule, a tablet, a coat tablet, and a capsule, ointment, patches, and suppositories, are mentioned, for example. In the case of pharmaceutical-preparation-izing, it can manufacture with a conventional method using the usual pharmaceutical preparation support.
[0023] That is, in order to manufacture oral pharmaceutical preparation, one or more sorts chosen from SACHIGURERU or aspirin or the salt of those permitted in pharmacology, an excipient, and after adding a binder, disintegrator, lubricant, a coloring agent, correctives, etc. if needed further, it considers as powder, a fine grain agent, a granule, a tablet, a coat tablet, a capsule, etc. with a conventional method.
[0024] As an excipient, a lactose, corn starch, white soft sugar, grape sugar, a mannitol, sorbitol, crystalline cellulose, a silicon dioxide, etc., for example as a binder For example, polyvinyl alcohol, polyvinyl ether, methyl cellulose, Ethyl cellulose, gum arabic, tragacanth, gelatin, a shellac, The hydroxypropyl methylcellulose, hydroxypropylcellulose, A polyvinyl pyrrolidone, polypropylene-glycol polyoxyethylene block polymer, meglumine, etc. as disintegrator For example, starch, an agar, the end of gelatin, crystalline cellulose, a calcium carbonate, A sodium hydrogencarbonate, calcium citrate, a dextrin, pectin, carboxymethyl-cellulose calcium, etc. as lubricant For example, what is permitted that magnesium stearate, talc, a polyethylene glycol, a silica, hardening vegetable oil, etc. add in drugs as a coloring agent is used for the menthol, aromatic powder, mentha oil, camphor Borneo, a cinnamomi cortex pulveratus, etc. as correctives in the end of cocoa. Of course, these tablets and granules are not hindered by coating suitably according to glycocalyx and other need.
[0025] Moreover, in case the pharmaceutical preparation for injection is manufactured, a solubilizing agent, a stabilizing agent, etc. are added to base resin pH regulator, a resolvent, an isotonizing agent, etc. and if needed, and it pharmaceutical-preparation-izes with a conventional method.
[0026] The approach at the time of manufacturing external preparations is not limited, but can be manufactured with a conventional method. That is, it is possible to use the various raw materials usually used for drugs, quasi drugs, cosmetics, etc. as a base ingredient used in pharmaceutical-preparation-izing.
[0027] As a base ingredient to be used, specifically For example, animal and vegetable oils, straight mineral oil, ester oil, Waxes, higher alcohol, fatty acids, silicone oil, a surfactant, Although raw materials, such as phospholipid, alcohols, polyhydric alcohol, water soluble polymers, clay minerals, and purified water, are mentioned and pH regulator, an anti-oxidant, a chelating agent, a preservation-from-decay antifungal agent, a coloring agent, perfume, etc. can be added further if needed The base ingredient of the external preparations concerning this invention is not limited to these. Moreover, components, such as the component which has other differentiation-inducing operations if needed, a blood-flow accelerator, a germicide, an antiphlogistic, a cell activator, vitamins, amino acid, a moisturizer, and a keratolytic drug, can also be blended. In addition, the addition of the above-mentioned base ingredient is an amount which becomes the concentration usually set up in manufacture of external preparations.

[0028] Although they differs, and is not limited by the existence of a symptom, severity, age, complication, and salt formation etc. and changes with the class, routes of administration, etc. of a salt, SACHIGURERU in this invention or the clinical dose of aspirin is usually 0.01mg - 2000mg of adult 1 Japanese hits, it is 0.1mg - 1500mg preferably, is 1mg - 1000mg still more preferably, and carries out dermal administration of this as suppositories in taking orally and a vein.
[0029] Next, as an example of representation of this invention compound, the example of pharmaceutical preparation of the tablet which makes SACHIGURERU an active principle, and the pharmaceutical preparation for injection is shown as an example. However, it cannot be overemphasized that the example of this invention is not limited to these.
[0030]
[Example]
Example 1 According to the tablet following formula of SACHIGURERU, the tablet of SACHIGURERU was obtained with the conventional method.
[0031]
[A table 2]
1錠中の組成（単位：mg）

サチグレル	1.0
マンニトール	適量
トウモロコシデンプン	10.0
結晶セルロース	10.0
ヒドロキシプロピルセルロース	2.5
カルボキシメチルカルシウム	3.8
ステアリン酸カルシウム	0.2

[0032] Example 2 The pharmaceutical preparation following formula for injection of SACHIGURERU was dissolved in distilled water for injection or a physiological saline, pH was adjusted by the citric acid, subsequently, after sterile filtration, it freeze-dried and the pharmaceutical preparation for injection was obtained.
[0033]
[A table 3]
1バイアル中の組成（単位：mg）

サチグレル・ナトリウム	1.0
マンニトール	1.0
クエン酸	適当量

[0034] Next, in order to show the effectiveness of this invention, the example of a vascularization depressant action trial of SACHIGURERU is hung up as an example of representation.
[0035]
[Effect of the Invention]
(The experiment approach)
(1) It dissolved in distilled water for injection, and the pharmaceutical preparation for SACHIGURERU injection obtained in the test compound aforementioned example 2 was used for the trial.
[0036] (2) the experiment design approach Asano ** -- it carried out based on the approach (Bull.Inst.Publ.Health, 12:34-44, 1963.). A detail is shown below. As a subject animal, 21 with a weights [2500-3000g] mature rabbits were divided into 5-6 groups and four groups, and drum immobilization was carried out under no anesthetizing at the natural prone position. The ear pinna was shaved after fixing a rabbit to a metallic drum, and it anesthetized by pentobarbital (40mg/(kg)). Next, the part which, if possible, approaches the arcade currently formed in right and left by branching was circularly pierced by the special puncher as a wearing part of an observation port, and subsequently,

among the perimeter, the ear-pinna artery centralis exfoliated in dull, and excised the skin of - outside in small Metz (a diameter [of 6mm] phix depth of 100 micrometers). After having inserted with the transparence acrylic board from ear-pinna both sides, building the observation port and pouring in a physiological saline, it fixed with the screw. On the other hand, in the microscope for observation, the vasoganglion which appears a photograph and video equipment in installation and an observation port was observed. After that, once per, the control group (n= 6) was medicated with the physiological saline day, and this invention compound group (every n= 5) was medicated with SACHIGURERU sodium (0. 6, 1.7, and 17 microg/kg) for three weeks, respectively. Observation assessment of whenever [new / of a blood vessel] was carried out with the image analyzer for three weeks.

[0037] (3) The result of having compared with it of a physiological saline administration group the rate of the new vasoganglion which occupies SACHIGURERU sodium (0. 6, 1.7, and 17 microg/kg) in the chamber of the group prescribed for the patient, respectively as a result test compound was shown in a table 4 and drawing 1 . (Average ** standard deviation shows, respectively.)

[0038]

[A table 4]

日	サチグレル投与量 (μg/Kg) 0 対照群 (n=6)	0.6 (n=5)	1.7 * (n=5)	17.0 ** (n=5)
8	12.1±12.1	14.6± 5.5	8.4± 7.3	2.3± 2.3
9	30.0±14.5	24.8± 7.4	15.6±10.6	5.8± 5.8
10	46.6±12.8	37.1± 7.9	27.6±13.4	17.6±13.1
11	58.9±11.3	47.3± 9.2	38.8± 9.6	28.4±12.1
12	69.0± 9.6	60.6± 8.6	47.2± 7.6	37.1±10.8
13	81.1± 8.6	73.6± 9.3	55.1± 6.9	45.3±10.5
14	89.4± 7.7	80.5± 7.8	64.9± 9.3	52.7± 9.9
15	94.0± 6.3	86.7± 8.0	75.8±12.8	60.8±10.5
16	96.9± 4.6	91.7± 6.4	81.3±13.1	70.3± 6.8
17	98.6± 2.8	96.0± 4.2	85.4±13.0	72.0±10.4
18	99.6± 0.7	98.5± 2.3	88.2±10.8	76.8±10.8
19	99.9± 0.1	99.6± 0.9	90.9± 8.3	79.9±10.9
20	100	99.9± 0.3	94.0± 7.0	83.0±10.3
21	100	100	95.3± 5.6	85.1±10.7

曲線下面積群間比較検定法 * ; P<0.05、** ; P<0.01

[0039] the control group which prescribed the physiological saline for the patient so that clearly from a table 4 and drawing 1 -- comparing -- SACHIGURERU sodium 1.7microg/kg or -- 17microg/kg By the group prescribed for the patient, the vascularization was controlled intentionally. (Area under the curve comparative assay between groups; $p< 0.05$, $p< 0.01$) Therefore, the compound concerning this invention In accordance with the safety being very high, are based on the depressant action of the high vascularization of clinical top usefulness. It was shown that it can become prevention and therapy / improvement agents, such as gastric cancer, lung cancer, hepatic carcinoma, colon cancer, colon cancer, rectal cancer, a pancreatic cancer, a prostatic cancer, vesical cancer, kidney cancer, an ovarian cancer, a

uterine cancer, a breast cancer, skin carcinoma, malignant **** or a basal cell carcinoma, keloid, inflammation, or diabetic retinopathy.
[0040]

[Translation done.]